The rejection of Claims 1-12 and 18-25 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. It was asserted in the Office Action that the specification, while being enabling for some types of cancer, does not reasonably provide enablement for all cancers.

The statutory basis for enablement is found in 35 USC § 112, paragraph 1 which provides in part that:

> . . . The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and use the same...

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. Genentech, Inc. v Novo Nordisk, A/S, 108 F. 3d 1361, 1365, 42 US PQ 2d 1001, 1004 (Fed. Cir 1997) (quoting In re Wright, 999 F. 2d 1557), 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see Hybritech, Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), which in this application is March 12, 2001. As the CAFC noted in Enzo Biochem, Inc. v. Calgene, Inc., (98-1438), a patent specification complies with the statute even if a reasonable amount of routine experimentation is required in order to practice a claimed invention but that experimentation must not be "undue" in quoting Wands, 858 F. 2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation...") The key word appears to be "undue" not "experimentation".

Applicant contends that the amount of experimentation required to carry out and practice the method recited in Claims 1-12 and 18-25 is not undue and that the specification fulfills the requirements of 35 USC § 112, paragraph one. The Office Action does not set forth a single instance where the specification fails to provide such enablement. In addition, the Office Action does not provide any evidence of any such undue experimentation other than an unsubstantiated assertion. As such the rejection is impermissible and cannot stand.

The test for undue experimentation is not merely quantitative, as noted in Calgene, supra since a considerable amount of experimentation is legally permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed to enable the determination

of how to practice desired embodiments of the claimed invention. Applicant contends that the tests of Calgene, supra, are met in that the experimentation is routine given the guidance provided herein. The amount of information and enablement is sufficient to satisfy 35 USC § 112, paragraph one.

The field of cancer treatment in dogs is a specialized field and those of skill in that art can readily practice the claimed invention by reading the specification including the details of the Example provided on pages 11 to 15. While an example is not required in a specification, a detailed Example is provided in this specification on pages 11-15.

Page 6, second paragraph of the application explains:

$1,25(OH)_2D_3$ treatment of SCC 2/88 cells leads to a diminished response to TGF-β. Treating SCC 2/88 cells with TGF-β alone leads to a 2- to 20-fold increase in levels of PTHrP mRNA after 24 hrs. However, treatment of SCC 2/88 with TGF-β plus $1,25(OH)_2D_3$ leads to an increase in PTHrP mRNA levels of only 1- to 3-fold over that of treatment with $1,25(OH)_2D_3$ alone.

Page 6, lines 13-16 of the application explains:

> "Levels of PTHrP mRNA in cells treated with with $1,25(OH)_2D_3$ and TGF-β, however, increased less than in cells treated with TGF-β alone. Cell treated with $1,25(OH)_2D_3$ and TGF-β show 1- to 3-fold higher PTHrP mRNA levels than cells treated with $1,25(OH)_2D_3$ alone."

Patent applications are not required to exemplify every species encompassed by their claims, even in an unpredictable art such as this. The specification provides sufficient disclosure through both an illustrative example and technology to practice the claimed invention. In addition, more than sufficient detail is provided in the specification to enable those of skill in the art to understand and practice the recited method. Thus the recited method is enabled.

For the reasons set forth above, Claim 1 is submitted to overcome the Section 112 rejections.

Claims 2-11 and 18-25 depend, directly or indirectly, from independent Claim 1. When the recitations of Claims 2-11 and 18-25 are considered in combination with the recitations of Claim 1, Applicant submits that dependent claims 2-11 and 18-25 likewise are patentable. The rejection of these claims is likewise overcome and should be withdrawn.

For the reasons set forth above, Applicant respectfully requests that the Section 112 rejections of Claims 1-12 and 18-25 be withdrawn.

The rejection of Claims 1-12 and 18-25 under 35 U.S.C. § 101 is respectfully traversed. It was asserted in the Office Action that the method recited in the claims lacks a credible utility.

Applicant contends that the specification provides a credible utility. Such credibility is established, at least, in the recitation of the Example on pages 11-15. Further, the Office Action failed to provide evidence that one of ordinary skill in the art would reasonably conclude that the specification did not possess the required utility. As such the burden does not shift to the applicant to provide any rebuttal evidence sufficient to convince such a person of the asserted utility. The specification contains sufficiently detailed information regarding the treatment of cancer that the Examiner cannot establish a sustainable reason to doubt the claimed invention's utility.

For the reasons set forth above, Claim 1 is submitted to overcome the Section 101 rejections.

Claims 2-12 and 18-25 depend, directly or indirectly, from independent Claim 1. When the recitations of Claims 11-12 and 18-25 are considered in combination with the recitations of Claim 1, Applicant submits that dependent claims 11-12 and 18-25 likewise are patentable.

For the reasons set forth above, Applicant respectfully requests that the Section 101 rejections of Claims 1-12 and 18-25 be withdrawn.

The rejection of Claims 1-5, 7-12 and 23-25 under 35 U.S.C. § 103 as being unpatentable over Boggolini et al. (US Patent No. 5, 087, 619) and Yu et al.(PMID 7756673) is respectfully traversed.

Claim 1 recites: A method of treating cancer in a dog, comprising the step of feeding the dog a therapeutic agent comprising a Vitamin D analog.

Boggolini et al. teaches a method of treating leukemia and basal cell carcinoma in a warm-blooded animal comprising administering an effective amount of a Vitamin D analog. Boggiolini et al. fails to teach or suggest treating a dog for cancer with a Vitamin D analog as claimed by applicant. Thus the method recited in Claim 1 is patentable over Boggolini et al.

Yu et al. describes examinations conducted with respect to a human cell line and reports that they have examined the in vitro effects of 1,25 dihydroxy-vitamin D3 1,25 (OH) $_2D_3$ and of two side chains analogs of $1,25(OH)_2D_3$ (EB1089 and MC903) on cell growth and parathyroid hormone related peptide (PTHRD) production in immortalized (HPK1A) and neoplastic (HPK1A-ras) keratinocytes. Applicant respectively submits that there is nothing in Yu et al. which teaches or suggests the method recited in Claim 1. In addition, Yu et al. fails to mention the SCC 2/88 cell line for which applicant has provided evidence of such cancer treatment in dogs. Thus the claimed invention is patentable over Yu et al.

Claims 2-5, 7-12, and 23-25 depend, directly or indirectly, from independent Claim 1. When the recitations of Claims 2-5, 7-12 and 23-25 are considered in combination with the recitations of Claim 1, Applicant submits that dependent claims 2-5, 7-12 and 23-25 likewise are patentable.

The Examiner's combination of Boggolini et al. with Yu et al. is traversed since there is no teaching nor suggestion in either Boggolini et al. nor Yu et al. for the combination. Further, Yu et al. pertains to a human cell line and specifically reports that they have examined the in vitro effects of 1,25 dihydroxy-vitamin D3 [1,25 (OH) $_2D_3$] and of two side chains analogs of 1,25 (OH) $_2D_3$ (EB1089 and MC903)) on cell growth and PTHRD production in immortalized (HPK1A) and neoplastic (HPK1A-ras) human keratinocytes.

Even if Boggolini et al. is combined with Yu et al., the resulting combination does not teach nor suggest the method recited in Claim 1, specifically, treating cancer in a dog with Vitamin D analog, the dosages recited in the claims, and the recited pharmaceutical excipients and auxiliaries.

In addition, Applicant respectfully submits that the Examiner's Section 103 rejection of presently pending claims 1-5, 7-12 and 23-25 is not a proper rejection. Obviousness cannot be established by merely suggesting that it would have been obvious to one of ordinary skill in the art to modify Boggolini et al. according to the teachings of Yu et al.

More specifically, as is well established, obviousness cannot be established by combining the teachings of the cited art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. The required teaching, suggestion and incentive supporting the Examiner's combination is absent here. Neither Boggolini et al. nor Yu et al. teach or suggest the claimed combination. Furthermore, in contrast to the assertion within the Office Action, Applicant respectfully submits that it would

not be obvious to one skilled in the art to combine Boggolini et al. with Yu et al. because there is no motivation to combine these references suggested in the art. Rather, the Examiner has not pointed to any prior art that teaches or suggests combining the disclosures.

As the Federal Circuit has recognized, obviousness is not established merely by combining references having different individual elements of pending claims. Ex parte Levengood, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). MPEP 2143.01. Rather, there must be some suggestion, outside of Applicants' disclosure, in the prior art to combine such references, and a reasonable expectation of success must be both found in the prior art, and not based on Applicants' disclosure. In re Vaeck, 20 U.S.P.Q.2d 1436 (Fed. Cir. 1991). In the present case, neither a suggestion nor motivation to combine the prior art disclosures, nor any reasonable expectation of success has been shown. Specifically, the Examiner has not pointed to any prior art that teaches or suggests a reasonable expectation of success or motivation in combining the references.

Furthermore, it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the cited art so that the claimed invention is rendered obvious. Specifically, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the art to deprecate the claimed invention. Further, it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. The present Section 103 rejection is apparently based on a combination of teachings selected from multiple patents in an attempt to arrive at the claimed invention.

Since there is no teaching, suggestion, or motivation in the cited references for the claimed combination recited in Claims 1-5, 7-12 and 23-25, the Section 103 rejection of Claims 1-5, 7-12 and 23-25 appears to be clearly based on an impermissible hindsight reconstruction in which isolated disclosures have been picked and chosen in an attempt to deprecate the present invention. Of course, such a combination is impermissible.

For at least the reasons set forth above, Applicant respectfully requests that the Section 103 rejections of Claims 1-5, 7-12 and 23-25 is overcome and should be withdrawn.

The rejection of Claims 6 and 18-22 as being unpatentable under 35 U.S.C. § 103 over Boggolini et al. and Yu et al. in view of Katzung is respectfully traversed.

Claims 6 and 18-22 depend from Claim 1. For the reasons set forth above, Claim 1 is submitted to be patentable over Boggolini et al. in view of Yu et al. Applicant submits that Katzung teaches that hypercalcemia causes central nervous system depression, including coma and is potentially lethal. Its major causes (other than thiazide therapy) are hyperparathyroidism and cancer with or without bone metastases. Further Katzung teaches that less common causes are hyperitiaminosis D, sarcoidosis, thyrotoxicosis, mil-alkali syndrome, adrenal insufficiency and immobilations. Katzung appears to be a non-analogous reference since Katzung does not relate to a method of treating cancer in a dog, comprising the step of feeding the dog a therapeutic agent comprising a Vitamin D analog, as recited in Claim 1. Therefore, Claim 1 is submitted to be patentable over Boggolini et al. and Yu et al. in view of Katzung.

When the recitations of Claims 6 and 18-22 are considered in combination with the recitations of Claim 1, Applicant submits that dependent claims 6 and 18-22 likewise are patentable.

In addition, the combination of Boggolini et al. and Yu et al. with Katzung is respectfully traversed as there is no teaching nor suggestion in Boggolini et al, Yu et al. or Katzung to combine Boggolini et al. and Yu et al. with Katzung. Thus the Examiner's rejection should be withdrawn.

Moreover even if Boggolini et al. is combined with Yu et al. and Katzung the resulting combination does not teach or suggest the methods recited in Claims 6 and 8-22. Thus the rejection should be withdrawn.

Applicants respectfully submit that the Examiner's Section 103 rejection of the presently pending Claims 6 and 18-22 is not a proper rejection. Obviousness cannot be established by merely suggesting that it would have been obvious to one of ordinary skill in the art to modify Boggolini et al. and Yu et al. according to the teachings of Katzung. More specifically, as is well established, obviousness cannot be established by combining the teachings of the cited art to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. The required teaching, suggestion and incentive supporting a combination is absent here. Neither Boggolini et al. nor Yu et al. teach or suggest the claimed combination. Furthermore, in contrast to the assertion within the Office Action, Applicant respectfully submits that it would not be obvious to one skilled in the art to combine Boggolini et al., Yu et al. and Katzung because there is no motivation to combine

the references suggested in the art. Rather, the Examiner has not pointed to any prior art that teaches or suggests combining these pieces of prior art.

As the Federal Circuit has recognized, obviousness is not established merely by combining references having different individual elements of pending claims. Ex parte Levengood, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). MPEP 2143.01. Rather, there must be some suggestion, outside of Applicant's disclosure, in the prior art to combine such references, and a reasonable expectation of success must be both found in the prior art, and not based on Applicant's disclosure. In re Vaeck, 20 U.S.P.Q.2d 1436 (Fed. Cir. 1991). In the present case, neither a suggestion or motivation to combine the prior art disclosures, nor any reasonable expectation of success has been shown. Specifically, the Examiner has not pointed to any prior art that teaches or suggests a reasonable expectation of success or motivation in combining the references.

Furthermore, it is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the cited art so that the claimed invention is rendered obvious. Specifically, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the art to deprecate the claimed invention. Further, it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. The present Section 103 rejection is apparently based on a combination of teachings selected from multiple patents in an attempt to arrive at the claimed invention.

Since there is no teaching, suggestion, or motivation in the cited references for the claimed combination recited in Claims 6 and 18-22 the 35 USC § 103 rejection of Claims 6 and 18-22 appears to be clearly based on impermissible hindsight reconstruction in which isolated disclosures have been picked and chosen in an attempt to deprecate the present invention. Of course, such a combination is impermissible, and for this reason, Applicant requests that the 35 USC § 103 rejection of Claims 6 and 18-22 be withdrawn.

Hardman et al., while not applied in the Office Action, is cited by the Examiner as teaching that pain is commonly associated with cancer. Hardman et al. appears to be non-analogous art and Applicant submits that the claimed invention is patentable over Hardman et al.

It is believed that all pending claims are in condition for allowance for at least the reasons set forth above. The elements recited in the pending claims are not taught nor suggested in the art asserted in the Office Action and thus all claims are deemed to be patentable. The patentability of each dependent claim on its own merits is respectfully requested since each dependent claim is also deemed to define an additional aspect of the invention requiring consideration or reconsideration, as the case may be.

In view of the foregoing amendments and remarks, all claims now active in this application are believed to be in condition for allowance. Reconsideration is requested along with early passage to issue. Favorable action and allowance are respectfully solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Nongnuch Inpanbutr

Art Unit: 1617

Serial No.: 09/804,111

Examiner: Mojdeh Bahar

Filed: March 12, 2001

For: EFFECTS OF 1,2,5 $(OH)_2D_3$ AND ITS ANALOGS ON PARATHYROID HARMONE-RELATED SECRETION AND CELL GROWTH IN CANINE SQUAMOUS CELL CARCINOMA

SUBMISSION OF MARKED UP SPECIFICATION AND CLAIMS UNDER 37 C.F.R. 1.121(c)(1)(ii).

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith are marked up Claims in accordance with 37 C.F.R. 1.121(c)(1)(ii) wherein additions are underlined and deletions are [bracketed].

2. (once amended) The method of claim 1 wherein the vitamin D analog is selected from the group consisting of 1α,25-$(OH)_2D_3$, 1α,25-$(OH)_2$-16-ene-23-yne-D_3 [analog V], and 1α,25-$(OH)_2$-22,24-diene-24,26,27-trihomo-D_3 [EB 1089] and stereoisomers thereof.

4. (once amended) The method of claim 2, wherein the vitamin D analog is 1α,25-$(OH)_2$-16-ene-23-yne- D_3 [analog V] and stereoisomers thereof.

5. (once amended) The method of claim 2, wherein the vitamin D analog is 1α,25-$(OH)_2$-22,24-diene-24,26,27-trihomo-D_3 [EB 1089] and stereoisomers thereof.

18. (once amended) The method of claim 1 wherein the Vitamin D analog is administered in combination with a bone agent comprising at least one of conjugated estrogens, conjugated estrogen equivalents, anti-estrogens, calcitonin, bisphosphonates, calcium supplements, calcium receptor agonists, cobalamin, pertussis toxin, boron, dehydroepiandrosterone [DHEA], activin and bone morphogenic protein.

19. (once amended) The method of claim 1 wherein the Vitamin D analog is administered in combination with a cytotoxic agent comprising at least one of estramustine phosphate, prednimustine, cisplatin, 5-fluoro-uracil, melphalan, hydroxyurea, mitomycin,

idarubicin, methotrexate, adriamycin, daunomycin, cyclophosphamide, doxorubicin [(hydroxydaunor ubicin)], vincristine [concouin] and pregnisone.

24. (once amended) The method of claim 23 wherein the pharmaceutically acceptable organic carrier substance and the pharmaceutically acceptable inorganic carrier substance include at least one of water, salt [buffer] and buffer solutions, alcohols, gum arabic, mineral and vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, and polyvinyl pyrrolidone.

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